INTERNATIONAL SEARCH REPORT

Inter...onal application No.
PCT/EP 99/04105

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Insofar as claims 18-40 may be intended as to be directed to methods to be practised on the human/animal body, then objection arises under Rule 39.1.iv PCT (subject matter under Article 17.2.a.i. PCT), therefore the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04105

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/705 C12N15/00 C07K16/28 A61K38/00 A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	EP 0 909 816 A (SANKYO CO) 21 April 1999 (1999-04-21) abstract examples	1-9, 12-20, 22,23, 25-40
X	WO 95 13701 A (LXR BIOTECHNOLOGY INC ;BARR PHILIP J (US); SHAPIRO JOHN P (US); KI) 26 May 1995 (1995-05-26) abstract disclosure figure 4	1-9, 12-20, 22,23, 25-40

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 1999	11/11/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Panzica, G

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/04105

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 10, 31 October 1997 (1997-10-31) & JP 09 166593 A (IGAKU SEIBUTSUGAKU KENKYUSHO:KK), 24 June 1997 (1997-06-24) abstract	1-9, 12-20, 22,23, 25-40
A	DE 195 44 332 A (DEUTSCHES KREBSFORSCH) 5 June 1997 (1997-06-05) the whole document	1-40
A	WO 98 08965 A (GENESIS RESEARCH & DEV CORP LI) 5 March 1998 (1998-03-05) the whole document	1-40
A	EP 0 716 095 A (ORIENTAL YEAST CO LTD) 12 June 1996 (1996-06-12)	1-40
X,P	EP 0 866 131 A (SANKYO CO) 23 September 1998 (1998-09-23) abstract examples	1-9, 12-20, 22,23, 25-40

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/04105

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0909816 A	21-04-1999	AU 5970198 A	08-10-1998
		CA 2233783 A	01-10-1998
		CN 1207395 A	10-02-1999
		CZ 9800985 A	14-10-1998
		HU 9800744 A	01-02-1999
		JP 11171900 A	29-06-1999
		NO 981454 A	02-10-1998
		NZ 330095 A	23-12-1998
		PL 325667 A	12-10-1998
		ZA 9802719 A	30-09-1998
WO 9513701 A	26-05-1995	US 5663070 A	02-09-1997
		AU 1056995 A	06-06-1995
		CA 2176575 A	26-05-1995
		EP 0729300 A	04-09-1996
		JP 9510864 T	04-11-1997
		US 5652210 A	29-07-1997
JP 09166593 A	24-06-1997	NONE	
DE 19544332 A	05-06-1997	WO 9720067 A	05-06-1997
		EP 0870061 A	14-10-1998
WO 9808965 A	05-03-1998	US 5912168 A	15-06-1999
		AU 4036797 A	19-03-1998
EP 0716095 A	12-06-1996	JP 8157500 A	18-06-1996
		CA 2164374 A	09-06-1996
EP 0866131 A	23-09-1998	AU 5937598 A	15-10-1998
		CA 2232828 A	21-09-1998
		CZ 9800858 A	14-10-1998
		HU 9800613 A	01-02-1999
		JP 10324699 A	08-12-1998
		NO 981272 A	22-09-1998
		NZ 330004 A	28-10-1998
		PL 325457 A	28-09-1998
		ZA 9802371 A	28-09-1998

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 16 February 2000 (16.02.00)	
International application No. PCT/EP99/04105	**Applicant's or agent's file reference** SMW/FP5781810
International filing date (day/month/year) 15 June 1999 (15.06.99)	**Priority date** (day/month/year) 18 June 1998 (18.06.98)
Applicant CHIODI, Francesca	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 January 2000 (13.01.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
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BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
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BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
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CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
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CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07K 14/00

A2

(11) International Publication Number: WO 99/65935

(43) International Publication Date: 23 December 1999 (23.12.99)

(21) International Application Number: PCT/EP99/04105

(22) International Filing Date: 15 June 1999 (15.06.99)

(30) Priority Data:

9813194.9	18 June 1998 (18.06.98)	GB
9905793.7	12 March 1999 (12.03.99)	GB

(71) Applicant *(for all designated States except US)*: KAROLINSKA INNOVATIONS AB [SE/SE]; S–171 77 Stockholm (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: CHIODI, Francesca [SE/SE]; Microbiology and Tumorbiology Center, Karolinska Institute, Doktorsringen 13, S–171 77 Stockholm (SE).

(74) Agents: WALTON, Seán, M. et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: FAS PEPTIDES AND ANTIBODIES FOR MODULATING APOPTOSIS

(57) Abstract

Anti–Fas (APO–1, CD95) autoantibodies are found in human sera, which antibodies are biologically functional. Peptide fragments of Fas recognised by such antibodies, and antibodies specific for such peptides, inhibit or promote apoptosis and cellular proliferation. Assay methods making use of Fas peptides or antibodies enable identification of further agents which modulate apoptosis and/or cellular proliferation.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 December 1999 (23.12.1999)

PCT

(10) International Publication Number
WO 99/065935 A3

(51) International Patent Classification[6]: C07K 14/705, C12N 15/00, C07K 16/28, A61K 38/00, 39/00

(21) International Application Number: PCT/EP99/04105

(22) International Filing Date: 15 June 1999 (15.06.1999)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

9813194.9	18 June 1998 (18.06.1998)	GB
9905793.7	12 March 1999 (12.03.1999)	GB

(71) Applicant *(for all designated States except US)*: **KAROLINSKA INNOVATIONS AB** [SE/SE]; S-171 77 Stockholm (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **CHIODI, Francesca** [SE/SE]; Microbiology and Tumorbiology Center, Karolinska Institute, Doktorsringen 13, S-171 77 Stockholm (SE).

(74) Agents: **WALTON, Seán, M.** et al.; Mewburn Ellis, York House, 23 Kingsway, London WC2B 6HP (GB).

(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
17 April 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 99/065935 A3

(54) Title: FAS PEPTIDES AND ANTIBODIES FOR MODULATING APOPTOSIS

(57) Abstract: Anti-Fas (APO-1, CD95) autoantibodies are found in human sera, which antibodies are biologically functional. Peptide fragments of Fas recognised by such antibodies, and antibodies specific for such peptides, inhibit or promote apoptosis and cellular proliferation. Assay methods making use of Fas peptides or antibodies enable identification of further agents which modulate apoptosis and/or cellular proliferation.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
WALTON, Seán, M.
Mewburn Ellis
York House
23 Kingsway
London WC2B 6HP
ROYAUME-UNI

Date of mailing (day/month/year) 23 December 1999 (23.12.99)	
Applicant's or agent's file reference SMW/FP5781810	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP99/04105	15 June 1999 (15.06.99)	18 June 1998 (18.06.98)

Applicant
KAROLINSKA INNOVATIONS AB et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,IL,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CU,CZ,DE,DK,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,
   HU,ID,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,
   SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   23 December 1999 (23.12.99) under No. WO 99/65935

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
SMW/FP5781810		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/04105	15/06/1999	18/06/1998
Applicant		
KAROLINSKA INNOVATIONS AB et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[X] furnished subsequently to this Authority in written form.

[X] furnished subsequently to this Authority in computer readble form.

[X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] th text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of th **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] None of the figures.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes th invention.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/ 04105

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for th following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Insofar as claims 18-40 may be intended as to be directed to methods to be practised on the human/animal body, then objection arises under Rule 39.1.iv PCT (subject matter under Article 17.2.a.i. PCT), therefore the search has been carried out and based on the alleged effects of the compound/composition.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SMW/FP5781810		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/04105	15/06/1999	18/06/1998
International Patent Classification (IPC) or national classification and IPC C07K14/00		
Applicant KAROLINSKA INNOVATIONS AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 14 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13/01/2000	06.10.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Julia, P Telephone No. +49 89 2399 8410

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/04105

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-56 as originally filed

Claims, No.:

1-40 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has

been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:

see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. R asoned statement under Article 35(2) with regard to novelty, inventiv step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10-11
	No:	Claims	1-9, 12-40
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-40
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	18-40; see citations and explanations

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Additional remarks to item I :

A "Sequence Listing" has been filed with the present application. This "Sequence Listing" comprises SEQ ID No.: 1 to SEQ ID No.: 9 (pages 1-5).

2. Additional remarks to item II :

The priority documents pertaining to the present application were not available at the time of establishing this international preliminary examination report (IPER). Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (18.06.98).

3. Additional remarks under item IV :

The IPEA considers that the present set of claims does not fulfil the requirements of Rule 13 PCT.

According to Rule 13 PCT, an application shall relate to one invention only or to a group of inventions so linked as to form a **single** general inventive concept ("requirement of unity of invention"). The "single or common general inventive concept" among the different claimed peptides is considered to be their "ability to raise anti-Fas autoantibodies". However, this ability has not been clearly demonstrated for all of them (Table 1). The absence of this ability in at least one of these peptides would result in an objection under Rule 13 PCT for lack of unity. The claimed peptides are structurally unrelated (the fact that all of them are derived from the Fas molecule cannot be seen as an "inventive concept" as far as other peptides derived from the Fas molecule were already known and available from the prior art) and they have a different activity (stimulating or inhibiting apoptosis, degree or level of activity, etc...). Moreover, several of these peptides had already been anticipated in the prior art as well as their use for raising antibodies and uses thereof (see "Additional remarks under item V" below). Thus, the IPEA fails to see a "single or common general inventive concept" among them and raises an objection under Rule 13 PCT for these peptides.

In view of the presence of claims directed to generic peptides which do not necessarily need to have : (a) the "ability to raise anti-Fas autoantibodies", or (b) the ability to "modulate apoptosis and/or cellular proliferation", or (c) they do not even need to be derived from the Fas molecule (see paragraphs (ii)-(v) under "Additional remarks to item VIII" below), an objection under Rule 13 PCT for lack of unity would be raised even if all

the specific peptides of claims 3, 4, etc... share the ability to raise anti-Fas autoantibodies.

4. Additional remarks to item V :

The present application discloses anti-FAS (APO-1, CD95) autoantibodies (IgG and IgM, present in the blood sera from healthy donors) and the corresponding antigenic Fas peptide fragments (Fp5 G40-V59 induce apoptosis, Fp8 and Fp9 important for binding of FAS to its natural ligand FasL, Fp11 E100-C119 and Fp17 W160-V179 block apoptosis, Fp12 and Fp18). These anti-Fas autoantibodies are able to inhibit proliferation and to induce apoptosis of Jurkat leukemia T cells.

The following documents have been cited in the International Search Report (ISR) as being relevant for assessing the novelty and inventiveness of the claimed subject matter:

i) WO-A-95/13701 (**D1**) discloses the production of a (recombinant) Fas molecule lacking the transmembrane region (Fas[SPEC0808]TM) and variants thereof including substitutions, insertions and deletions. In fact the term Fas[SPEC0808]TM is defined as encompassing **all** the non- membrane-bound forms of the Fas molecule lacking TM (page 4, lines 16-18). Figure 4 shows four different (synthetic) Fas peptides which are said to be used for raising anti-Fas antibodies useful in the detection of biologically important Fas molecules (page 3, lines 15- 17) and which are further defined as encompassing regions in Fas[SPEC0808]TM that differs from Fas, TM region (page 9, lines 8-12). These Fas peptides consist of (i) H44-D56 (which overlaps with **Fp5** G40-V59 of the present application and it has one difference at position 45, L/K), (ii) N157-V172 and (iii) T174-V179 (which partially overlap with **Fp17** W160- V179) and (iv) T147-E152. D1 refers among other different uses of Fas[SPEC0808]TM to the its administration for competitively binding the FasL and preventing or decreasing the apoptotic signals of Fas (page 10, lines 21-25) as well as the reduction of (endogenous, native) Fas[SPEC0808]TM levels by exposure to anti-Fas[SPEC0808]TM antibodies, such as the ones raised against peptides (i)-(iv) (page 11, lines 35-36). Claim 9 of D1 is directed to a "substantially purified protein comprising" the peptides of Figure 4 and claim 14 to antibodies that specifically recognize Fas[SPEC0808]TM but not Fas. In view of this disclosure the IPEA considers that the subject matter of at least claims 1-9 and 12-40 has been anticipated (Articles 33 (2), (3) PCT) and that claims 10-11 do not comprise subject matter that could be seen as involving an inventive contribution (Article 33 (3) PCT).

ii) Patent Abstract of Japan (31.10.97) & JP-09 166593 (**D2**) refers to an immunological method and kit for measuring a Fas antigen. As a standard substance reference is made to a Fas antigen originating in WR19L-12a cell. The document also refers to two different anti-Fas antibodies, one raised against the "inner area of Fas-antigen" and one raised against the "outer area of Fas-antigen". No specific (Fas, Fas peptide, Fas fragment) sequence is disclosed in this document and there is no further information concerning the "standard" Fas antigen used and/nor the actual areas of the Fas antigen used for raising the antibodies. thus, in the absence of these information, the IPEA cannot assess the relevance of this document for the claimed subject matter. However, the general teachings of this document certainly anticipate the generic subject matter of at least claim 37.

iii) DE-A-19544332 (**D3**) discloses a method for determining the amount of mRNA CD95L (FasL) in a cell using a specific CD95L competitor which is derived from the same CD95L (short CD95L fragment comprising identical residues but with the insertion of several different residues in the middle region). The document does not disclose any generic Fas fragment/peptide let alone the specific ones disclosed in the present application.

iv) WO-A-98/08965 (**D4**) discloses regulatory DNA sequences (located in a 70 bp region about 1kb upstream from the coding region of CD95) that are able to enhance or silence the transcription of coding portions of the CD95 gene as well as CD95 protein transcription factors that bind to said regulatory sequences and thus, being able to modulate the (apoptotic) effects of CD95. However, there seems to be no disclosure of any generic Fas fragment/peptide let alone the specific ones of the present application.

v) EP-A-0 716 095 (**D5**) discloses the production of an anti-Fas antibody directed against the intracellular region of the Fas molecular. In particular, the document discloses the synthesis of a Fas peptide comprising the C-terminal of the intracellular region of the Fas molecule. This specific anti-Fas antibody allows to know the skilled person whether the soluble Fas molecule present in blood sera contains an intracellular region or has only an extracellular region (Fas form cut on the surface of a cell). A soluble Fas molecule with an intracellular region is said to be found in several diseases, such as in autoimmune diseases and rheumatoid arthritis. Even if this document does not disclose any of the specific peptides of the present application, the IPEA considers that it certainly anticipates the subject matter of at least claims 37 and 40. Furthermore, in view of the broad reference

to a generic "method of treatment" in claims 1-2 of the present application, the subject matter of these claims cannot be seen as inventive and thus, D5 would render the subject matter of at least claims 1-2, 10, 12-36 and 38-40 obvious (Article 33 (3) PCT).

Furthermore, the IPEA would like also to draw the attention of the Applicant to the following general points :

a) **D1** refers on page 2, lines 2-4 to the extracellular region of the Fas molecule as consisting of 157 residues and as being able to block the apoptosis caused by Fas-FasL, i.e. it is able to "modulate the apoptosis" in the sense of the present application. Such a Fas extracellular fragment would certainly comprise at least the peptides **Fp5** (G40-V59) and **Fp11** (E100-C119) of the present application. Thus, as far as the "length" of the claimed peptides as well as the length of the "Fas fragments" referred in the claims are not clearly defined in the claims (see paragraphs (iii)-(v) below under "Additional remarks to item VIII"), this Fas extracellular peptide (or arbitrary short fragments thereof, such as deletion variants, etc...) anticipates the broad subject matter of at least claims 1- 3, 5-8, etc...

b) on page 2, lines 30-32 of **D1** there is a reference to a prior art document (Oehm et al., 1991) which according to D1 discloses the presence of increased levels of anti-Fas autoantibodies in AIDS patients. No reference is made to the specific Fas antigenic regions responsible thereof. However, in case that these regions were known and they would overlap with regions of the claimed peptides, this prior art document would be relevant for assessing the novelty and inventiveness of the present set of claims.

c) on page 46 lines 7-9 of the present application reference is made to the fact that "...it has previously been shown that **Fp11** can block the apoptotic activity of CH-11 (Fadeel et al., 1995)...". The IPEA considers that this reference implies not only that the **Fp11** peptide was already know in the prior art but its ability for modulating the apoptosis as well. If this is the case, the cited prior art could be relevant for

d) according to the references cited in the present description and in particular Staling et al., 1997 and Fadeel et al., 1995, the skilled person was well aware of the relevance and importance of several specific residues of the Fas molecule (such as K84, L90, E93 and H126) for (sterically) allowing the binding Fas-FasL (allowing binding of FasL to residues

K86K87 of the Fas molecule). Thus, the IPEA considers that for blocking or decreasing the apoptotic effects of the Fas molecule it would have been evident to the skilled person to hinder this Fas-FasL binding and an obvious way for achieving this result would have been the production of specific antibodies against these known Fas regions involved in the binding, namely the region cited above, i.e. at least K84-E93 or K84-H126. For raising such specific antibodies, these peptides would have to be in a way produced, isolated or synthetised, in other words they would have to be made available to the skilled person. Thus, the peptide K84-H126 would have comprised the sequence of at least the peptide **Fp11** of the present application.

The attention of the Applicant is also drawn to the fact that the subject matter of claims 18-34 is directed to methods for treatment of the human or animal body (insofar as the claimed subject matter comprises or embraces methods that can be carried out in vivo too) and thus, it may be excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT too. Furthermore, for such a subject matter no unified criteria exist in PCT for the assessment whether it is industrially applicable or not. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5. Additional remarks to item VI :

Certain published documents (**Rule 70.10 PCT**) : EP-A1-0909816, publication date: 21.04.99, priority dates: 01.04.97, 25.06.97 and 08.10.97, filing date: 01.04.98; EP-A2-0 866 131, publication date: 23.09.98, priority date: 21.03.97, filing date: 20.03.98.

6. Additional remarks to item VII :

i) the following bibliographic references are differently given in the description and in the list of references provided by the Applicant : (a) Ju et al., 1997 on page 47, lines 3-4 whereas on page 54, line 14 is given as 1995; (b) Brunner et al., 1997 on page 47, line 3 whereas on page 54, line 1 is given as 1995; (c) Starling et al., 1997 on page 49, lines 6-7, 9 whereas on page 55, line 11 is given as 1977; and (d) Irmler et al., 1997 on page 50, line 24 whereas on page 54, line 14 is given as 1977.

ii) several bibliographic references found in the list given on pages 53-55 of the description have not been cited in the description. In particular : (i) Ellis and Atkinson 1996, (ii) Lutomski et al., 1995; (iii) Prabhakar et al., 1997; (iv) Rose and Bona 1993; (v) Song et al., 1996 and (vi) Vassilev et al., 1996

7. Additional remarks to item VIII :

The following objections are also raised under **Article 6 PCT** concerning the clarity of the claims :

i) according to Article 6 PCT, the claims shall be clear and concise. The requirement that the claims shall be concise refers to the claims in their entirety as well as to individual claims. The number of claims must be reasonable in relation to the nature of the invention claimed, and undue repetition of wording, for example between one claim and another, should be avoided by the use of dependent form (see PCT Gazette, 29.10.98, PCT International Preliminary Examination Guidelines, Section IV, III-5.1). The IPEA considers that the present set of claims contains a large number of claims (40) which further repetition of wording among them (4 independent claims directed to a peptide; 4 independent claims directed to assay methods, etc...).

ii) according to Article 6 PCT in combination with Rule 6.3 PCT too, the claims shall define the matter for which protection is sought in terms of technical features. The IPEA considers that a peptide, polypeptide, protein, oligonucleotide, gene, etc.. being chemical products must be clearly and unambiguously characterized by their amino acid and/or nucleic acid sequences, i.e. by reference to their specific SEQ ID No. The characterization of a product only by the desired function ("...modulates apoptosis and/or cellular proliferation...") does not fulfill the requirements of said Article 6 PCT in combination with Rule 6.3 PCT. Thus, claims directed to generic "Fas peptides" which are only characterized by the desired activity do not fulfil these requirements.

In fact, the application refers to the (simultaneous multiple solid-phase) synthesis of 20 amino acid long Fas peptides (with a 10-residue overlap) (pages 38-39) which, according to Table 1, only the peptides Fp5, Fp11, Fp12 and Fp17 show a clear reactivity with human serum of healthy donors, i.e. presence of autoantibodies against these peptides. Moreover,

on page 5 lines 13-15 it is further indicated that peptide 16 (Fp16) which presents an overlap of 10 residues with Fp17, has low or no reactivity with human sera. Therefore, in view of this information and the requirements of article 6 PCT in combination with Rule 6.3 PCT, the IPEA considers that the application clearly discloses eight specific peptides (i)-(viii) but that there is no basis for claims directed to generic "Fas peptides" (undue burden, no technical support, etc...). Thus, the subject matter of at least independent **claims 1, 5 and 7** as far as directed to generic "Fas peptides" (as well as claims dependent thereon) is considered to be defined only by the result desired to be achieved.

iii) the IPEA further considers that the wording of **claims 1-2** is ambiguous. The size of a "peptide" is not clearly defined in these claims and the wording "a fragment" is also open in the sense that it can be as shortly as consisting of only one or two residues. Several short peptides (dipeptides, etc...) have certainly been used in different methods of treatment (such as for instance deficiency of certain essential amino acids, etc...) and they will actually bear no technical relationship with the present application, namely the (a) being peptides derived from the Fas molecule and (b) being capable of producing a "...modulation of apoptosis and/or cellular proliferation...".

This objection is also relevant for **claim 3**, which by using the wording "comprises" is not actually restricted to the specific amino acid sequences cited in the claim. In fact, claim 3 includes (large) fragments of Fas which have certainly been used in a method of treatment of the human or animal body by therapy.

iv) the wording of **claim 5** is also considered to be ambiguous for the following reasons : (a) "up to about 40 amino acids" does not clearly define the length of the peptide (it could well be 60, 70,.... or else 10, 5... ???). There is no indication of the range of variability for both "up to" in combination with "about". Furthermore, (b) the peptide is defined as comprising "a fragment of Fas", i.e. it does not require that the peptide of "up to about 40 amino acids in length" is a fragment of Fas but it is enough to "comprise" a fragment of Fas, wherein such a fragment can again be as arbitrarily short as consisting of only one or two residues. Any peptide (of "...up to about 40 amino acids in length...") having the desired activity (being able to "...modulate apoptosis and/or cellular proliferation...") will certainly "comprise" a fragment of Fas (at least one or two residues thereof) which modulates apoptosis and/or cellular proliferation and thus, fall under the scope of the claim

(even if technically completely unrelated to Fas).

This objection is not overcome by the wording of **claim 6,** which only requires the "amino acid sequence of said fragment" (such as consisting of only one or two residues) to be found within an amino acid sequence selected from a specific group but not to be actually one of these (complete) specific sequences.

v) in view that the wording "up to about 40 amino acids in length" is considered to be ambiguous (see paragraph (iv) above) and that it is not clear whether the 80% similarity has to be for the complete claimed peptide or else for "...a contiguous sequence of at least 10 amino acids...", the IPEA considers that the wording of **claim 7** is not clear. In fact, the scope of this claim could comprise any peptide of 30, 40, 50, etc... amino acids in length, wherein only 8 contiguous amino acids thereof had a similarity with an arbitrarily chosen "fragment of Fas" (not even the ones disclosed in the application (i)-(viii) and related to the Fas activity), and having the desired activity ("...modulates apoptosis and/or cellular proliferation..."). Moreover, the wording "similarity" is also open to different interpretations (structurally conservative exchanges, functional invariable exchanges, etc...). The IPEA considers that the wording of this claim should be clear and it should unambiguously refer to the Fas peptides shown in the application to have the desired activity.

vi) the subject matter of both **claims 8 and 9** refers to the same type of peptides (any one of claims 1 to 7), however, the effect or function of these peptides in both claims is contrary, i.e. in claim 8 reference is made to **inhibition** of apoptosis, whereas in claim 9 reference is made to **stimulation** of apoptosis. The IPEA considers that in both claims it should be clearly specified which peptides of any one of claims 1 to 7 have the desired effect and/or activity (stimulation: peptide Fp5, inhibition: peptides Fp11 and Fp18 ??).

vii) the IPEA considers that as far as the wording of the claims 4 to 8, in particular claims 5-8, comprise peptides which are completely unrelated to the specific Fas peptides of the present application (see paragraphs (iv)-(v) above), the subject matter of at least independent **claim 18** (and all claims dependent thereon) is ambiguous and not clear. The peptides of claims 4-8 will not necessarily result in antibodies "...containing a binding site able to bind Fas..." and the skilled person will be unable to put into practice the claimed method. A similar objection applies for all claims related to antibodies defined through the

peptides of these claims 4-8 and for claims related to the use of these peptides for detecting/screening/producing said antibodies, such as at least for independent **claims 25-27, 29,** etc... (and dependent claims thereon).

viii) the reference to a non-disclosed "...conditions..." in **claim 27** is ambiguous. The reference to "...**a** candidate modulator..." in **claim 28** is ambiguous too. It should probably refer to "...**the** candidate modulator..." identified or obtained by a method according to any one of claims 25 to 27. Moreover, it seems to the IPEA that the order of administration of the different products (Fas positive cells with (a) a test substance and (b) an antibody molecule directed against a peptide according to any one of claims 4 to 8) in at least independent **claim 29** (and claims dependent thereon) is relevant for the successful performance of the claimed method. Several claims (such as **claim 30-32**, etc...), which are formally dependent on claims directed to "an assay method" (such as claim 29) do not actually seem to be directed to said "assay method" but more to a therapeutical method.

ix) several claims directly or indirectly concerned with therapeutic treatments do not clearly indicate the specific treatment disclosed in the application ("...modulates apoptosis and/or cellular proliferation...") and thus, they seem to worded in a broad and open manner such as for a first generic medical application not limited to the specific exemplified teachings of the present application (see in particular **claims 1-2, 35-36, 40**, etc...).

x) the attention of the Applicant is also drawn that the subject matter of **claim 37** is directed to any isolated human antibody "specific" (whatever it means) for human Fas and not to against the specific Fas fragments disclosed in the application. Moreover, the objection raised in paragraph (vii) above also applies for the wording of **claim 38**.

xi) the IPEA also considers that there is a serious inconsistency between the subject matter of the claims and the description. The description seems to include (a) broad interpretations for the actual meaning of several wording present in the claims as well as (b) many embodiments which appear to fall outside the subject matter actually covered by the claims (see PCT Gazette-Section IV, Special Issue, PCT International Preliminary Examination Guidelines, 29.10.98, paragraph C-III, 4.3). In particular on pages 5-6 a "peptide" is described as comprising variants, derivatives, mimetics, etc.... (with homologies/similarities as low as only 30%) which are only limited by the desired functionality ("...modulates apoptosis and/or cellular proliferation..."), on page 29 it is said

that the invention extends to a substance identified as a modulator of Fas activity, etc...

xii) the correspondence of the specific peptides in the claims (claims 3, 4, etc...) and the designation given in the description is not directly and clearly deduced from the present description. It seems to the IPEA that peptide (i) corresponds to Fp5, peptide (iv) to Fp11 and peptide (vi) to Fp17 and probably peptide (viii) corresponds to Fp18. However, it is not clear the correspondences among peptides (ii), (iii), (v), (vii) and Fp8, Fp9 and Fp12 (let alone the peptides further indicated in Table 1).

xiii) in view of the actual results shown in the present description, in particular in Table 1 and in Figures 1-3, the IPEA is willing to acknowledge that the specific Fas peptides Fp5, Fp11, Fp12 and Fp17 are able to raise anti-Fas autoantibodies (see paragraph (ii) above). However, in view of the results obtained with peptide 16 (page 5 of the application), the IPEA fails to see any clear demonstration showing that other specific Fas peptides, such as Fp18 and peptides (ii), (iii), (v), (vii) of claims 3, 4, etc..., actually possess such ability. Peptides Fp8 and Fp9 are shown in Table 1 to react with "commercially available Ig preparations derived from enriched pooled human serum". It is, however, not clear whether such a pooled blood is exclusively taken from healthy donors and any possible contamination is certainly excluded. Moreover, the reactivity of these peptides is similar to the one shown by Fp16, which according to page 5 of the description it has only a low or no reactivity at all with human serum, i.e. it has not been considered to be relevant . Thus, an objection under Article 6 PCT (support by the description) in combination with Article 5 PCT (clear and complete disclosure in the description) is raised for these peptides.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/13173

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A01N 43/04; A61K 31/70, 35/16, 39/00; C07H 17/00; C07K 14/00, 14/435, 14/47, 14/705, 16/00; C12N 1/00, 5/06, 15/00, 15/09, 15/12, 15/87; G01N 33/53

A. CLASSIFICATION OF SUBJECT MATTER:
US C :

435/6, 7.1, 7.2, 7.21, 172.1, 172.3, 240.2, 240.21, 320.1; 514/2, 44; 530/350, 387.1; 536/23.1, 23.5, 24.1; 800/2

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

Databases: APS, ANABSTR, AQUASCI, BIOBUSINESS, BIOSIS, BIOTECHDS, CA, CABA, CANCERLIT, CAPREVIEWS, CONFSCI, DISSABS, DRUGB, DRUGLAUNCH, DRUGNL, DURGU, EMBASE, FSTA, GENBANK, HEALSAFE, IFIPAT, JICST-E, JPNEWS, LIFESCIE, MEDLINE
Search Terms: Barr?/au; shaprio?/au; keifer?/au; fas; tm; transmembran?; membran?; solubl?; secret?; antibod?; transgen?; pcr; polymerase; chain; reaction; gene; therap?

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1-7, drawn to DNA, vectors and host cells comprising a gene encoding FasΔTM.

Group II, claim 8, drawn to transgenic animals comprising a gene for FasΔTM.

Group III, claims 9-13, 16 and 23, drawn to FasΔTM proteins and methods of using said proteins.

Group IV, claims 14, 15 and 17-19, drawn to antibodies that recognize FasΔTM and methods of using said antibodies.

Group V, claims 20-22, drawn to nucleic acids detection assays.

Group VI, claims 24-28, drawn to gene therapy methods using a gene for FasΔTM.

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of groups I-IV are distinct, one from the other because they are drawn to materially different compositions that require divergent areas of search, consideration and analysis and that may be used in materially different fashions. For example, the DNA of the invention of group I may be used to prepare recombinant proteins or for use as hybridization probes, which does not involve the in vivo considerations required for analysis of the genetic alteration of an animal,such as those of the invention of group II. The DNA of group I also represents a materially different composition than that of the proteins of group III (comprised of amino acids rather than nucleic acids) and comprises a distinct activity than that of an antibody (group IV) which is a specific, protein based binding reagent). Thus, each of the compositions of the inventions of groups I-IV represent distinct chemical compounds with divergent uses that require disparate considerations based upon their chemical and biological properties.

The inventions of group I and either of the inventions of groups V or VI are distinct, one from the other because the DNA of group I may be used in materially different fashions as evidenced by its use in the detection assays of group V and the therapeutic application of the invention of group VI.

The inventions of groups II-IV and either of the inventions of groups V or VI are distinct, one from the other because the former groups of compositions comprise proteins which are not utilized in the methods of groups V and VI that are based upon nucleic acids.

The methods of groups V and VI are distinct, one from the other because they are drawn to materially different methods that require divergent areas of search and consideration. In the case of the invention of group VI, the methods are directed to in vivo gene therapy which require consideration of means of administration, targeting and expression and exogenous nucleic acids while the methods of group V are predicated upon in vitro diagnostics which do not include in vivo considerations.

For the reasons stated above, the listed groups of inventions are not so linked by any special technical feature within the meaning of PCT Rule 13.2 so as to comprise a single inventive concept.